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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

REVIEWER

FEB - 1 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Fenpropathrin.** Review of a Metabolism Study and a Dermal Absorption Study.

EPA ID# 059639-00076 DP Barcode: D210567
PC No. 127901 Case No. 052153

FROM: John E. Whalan, D.A.B.T., Senior Toxicologist
Section 1, Toxicology Branch I
Health Effects Division (7509C)

John E. Whalan 10-6-95

TO: George LaRocca (PM Team #13)
Registration Division (7505C)

THRU: Roger L. Gardner, Section Head
Section 1, Toxicology Branch I
Health Effects Division (7509C)

Roger Gardner 1/23/96 KB 1/26/96

I. Background: The following two studies were performed at the request of the State of California. Valent has submitted these studies to the HED for review. Neither study was needed to fulfill a data gap.

Dermal Absorption of ^{14}C-Fenpropathrin in DANITOL® Using Male Sprague-Dawley Rats.; Study No. Battelle SC900017; February 15, 1991; MRID No. 434338-01.

Excretion, Distribution and Metabolism of [^{14}C]S-3206 Following Single or Multiple Dose Administration to Rats.; Study Nos. 91-0238 and 3993-91-0238-AM-002; June 13, 1994; MRID No. 434768-01.

The new dermal absorption study conforms to the EPA Guideline 85-2 (1994). The metabolism study conforms to current guidelines regarding the number of animals and dose levels, and the ^{14}C-labelling of both the acid and alcohol.

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II. Recommendations and Conclusions:

Dermal Absorption: Although a dermal absorption study has never been required, one was reviewed in 1988 and classified **Acceptable** (MRID No. 00163822). The new study, which is classified **Acceptable** and satisfies data requirement 85-3, is superior to the previous study and replaces it in the Toxicology Profile (attached).

Male Sprague-Dawley (CD/BR) rats were dermally dosed with concentrations of 0.03%, 1.5%, and 30% (0.03, 1.5, and 30 mg/rat). These doses corresponded to a) the lowest concentration encountered by applicators in the field, b) the recommended field dilution, and c) the concentration found in Danitol 2.4 EC, respectively.

Fenpropathrin is readily absorbed through the skin of the rat. Mean dermal absorption between the 0.5 and 24 hour intervals was 34%, 22%, and 22% in the low, mid, and high-dose groups, respectively. Elimination is primarily through the urine, and secondarily through the feces. Absorption:elimination equilibrium was reached in as little as 4 hours at low doses (0.03%), and no more than 10 hours at higher doses (1.5% and 30%). The rates of elimination for the low, mid, and high concentrations were 0.88%/hour, 0.38%/hour, and 0.19%/hour in the urine; and 0.39%/hour, 0.13%/hour, and 0.029%/hour in the feces, respectively.

Metabolism: The metabolism study requirement had been satisfied by two Core Minimum studies (MRIDs No. 00126826 and 00130871) reviewed in 1985. The new study, which is **Acceptable** and satisfies data requirement 85-1, is superior to these older studies and is also included in the Toxicology Profile.

Elimination was similar in both sexes. The urine:feces ratio of elimination was 1:2 following a single dose of 2.5 or 25 mg/kg, and 1:1 following 15 daily doses. The half-life was 11-16 hours in the urine, and 7-9 hours in the feces. After 7 days, >99% of the administered dose was excreted. A small percentage of radiolabel was found in the tissues (mostly in the fat).

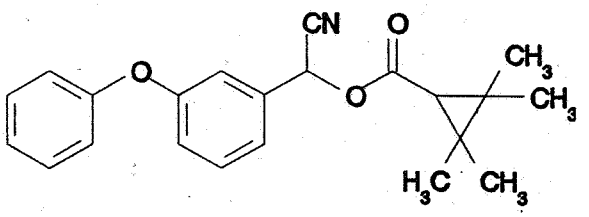
The major biotransformations included oxidation at the methyl group of the acid moiety, hydroxylation at the 4'- position of the alcohol moiety, cleavage of the ester linkage, and conjugation with sulfuric acid or glucuronic acid. The parent chemical was found in feces, but not in urine. Eight urinary metabolites and 4 fecal metabolites were identified.

III. Data Requirements and Data Gaps (CFR §158.35):

PC CODE: 127901

CASE NO.: N/A

REGISTRANT: Valent U.S.A.
(formerly Sumitomo Chemical Company)



REGISTERED USE PATTERNS: Two identical products are registered:
TAME® - Indoor greenhouse use as an insecticide and miticide on ornamental plants, shrubs, and trees including nonbearing apple and pear trees.
Danitol® 2.4 EC Spray - Agricultural use as an insecticide and miticide.

Technical: **Fenpropathrin** (S-3206; 91.9% a.i.) - a synthetic pyrethroid
Registration No. 59639-76

	Required	Satisfied	
81-1	Y	Y	Acute Oral Toxicity
81-2	Y	Y	Acute Dermal Toxicity
81-3	W	-	Acute Inhalation Toxicity
81-4	Y	Y	Primary Eye Irritation
81-5	Y	Y	Primary Dermal Irritation
81-6	Y	Y	Dermal sensitization
81-7	N	-	Acute Delayed Neurotoxicity (hen)
82-1a	Y*	Y	Subchronic Oral (rodent)
82-1b	Y*	Y	Subchronic Oral (nonrodent)
82-2	Y	Y	21-Day Dermal
82-3	N	-	90-Day Dermal
82-4	N	-	21-Day Inhalation (tobacco use)
82-4	N	-	90-Day Inhalation
82-5a	N	-	90-Day Neurotoxicity (hen)
82-5b	N	-	90-Day Neurotoxicity (mammal)
83-1a	Y	Y	Chronic Toxicity (rodent)
83-1b	Y	Y	Chronic Toxicity (nonrodent)

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	Required	Satisfied	
83-2	Y	Y	Carcinogenicity (two species)
83-3a	Y	Y	Developmental Toxicity (first species)
83-3b	Y	Y	Developmental Toxicity (second species)
83-4	Y	Y	Reproduction
83-5	Y†	Y	Chronic/Carcinogenicity (see 83-1 & 83-2)
84-2a	Y	Y	Mutagenicity - Gene Mutation
84-2b	Y	Y	Mutagenicity - Structural Chrom. Aberr.
84-2c	Y	Y	Mutagenicity - Other Genotoxic Effects
85-1	Y	Y	General Metabolism
85-2	N	Y	Dermal Penetration
86-1	N	-	Domestic Animal Safety

Y -Yes
N - No
W - Waived
P - Partially

* The requirement is satisfied if an acceptable chronic study is available.
† Required unless separate acceptable chronic and oncogenicity studies are available.

Formulation:	TAME® (33.59% a.i.; contains 2.4 pounds a.i./gallon and xylene range aromatic solvent). The name of this product was changed from Danitol® 2.4 EC Spray in order to distinguish it for ornamental uses. Registration No. 59639-77.

	Required	Satisfied	
81-1	Y	Y	Acute Oral Toxicity
81-2	Y	Y	Acute Dermal Toxicity
81-3	Y	Y	Acute Inhalation Toxicity
81-4	Y	Y	Primary Eye Irritation
81-5	Y	Y	Primary Dermal Irritation
81-6	Y	Y	Dermal Sensitization
82-2	Y	Y	21-Day Dermal

Formulation:	Danitol® 2.4 EC Spray (33.59% a.i.). This product is identical to TAME®, but is intended for agricultural uses. Registration No. 59639-35

Y -Yes
N - No
W - Waived
P - Partially

* The requirement is satisfied if an acceptable chronic study is available.
† Required unless separate acceptable chronic and oncogenicity studies are available.

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IV. Toxicology Profile:

Technical: **Fenpropathrin** (S-3206; 91.9% a.i.) - a synthetic pyrethroid
Registration No. 59639-76

	STUDY	RESULTS
81-1	**Acute Oral, Rat** Minimum / Toxicity Category I Study FT-50-0018; January 1979 HED Document No. 4567 MRID No. 00127343	LD_{50} = 54.0 (43.5-67.0) mg/kg, ♂ 48.5 (37.6-62.6) mg/kg, ♀ Clinical signs: Decreased spontaneous motor activity, hypersensitivity, fibrillation, tremor, clonic convulsions, salivation, lacrimation, incontinence, and hind limb ataxia.
81-2	**Acute Dermal, Rat** Minimum / Toxicity Category II Study FT-60-0019; January 1979 HED Document No. 4567 MRID No. 00127352	LD_{50} = 1600 (1150-2220) mg/kg, ♂ 870 (670-1120) mg/kg, ♀ Clinical signs: Deaths in 3 days, ataxia, and hypersensitivity.
81-3	**Acute Inhalation, Rat & Mouse** Minimum / Toxicity Category IV Study 2545; September 5, 1986 HED Document No. 7253 MRID No. 00163812	It was not possible to generate sufficient test article vapor or aerosol to elicit toxicity. The maximum attainable concentration (0.009 µg/l as vapor) was nontoxic. **NOTE:** The Registrant reports that the only time the technical can contaminate the atmosphere is when it is melted during formulation. Thus, vapor exposure was appropriate (John E. Whalan memorandum, dated February 26, 1987).
81-4	**Primary Eye Irritation, Rabbit** Guideline / Toxicity Category III Study FT-80-0023; January 1979 HED Document No. 4567 MRID No. 00127357	No corneal involvement. Mild iris and conjunctival irritation.
81-5	**Primary Dermal Irritation, Rabbit** Guideline / Toxicity Category IV Study FT-80-0023; January 1979 HED Document No. 4567 MRID No. 00127357	No irritation.
81-6	**Dermal Sensitization, Guinea Pig** Minimum Study FT-50-0024; July, 1979 HED Document No. 4567 MRID No. 00127358	Not a sensitizer.

82-1a	**3-Month Feeding, Rat** Minimum Study TLGR 0020.76; December 12, 1979 HED Document No. 4567 MRID No. 00127363	NOEL = 300 ppm (15 mg/kg/day) LEL = 600 ppm (30 mg/kg/day) - Body weight reduction (♀), body tremors, decreased kaolin-cephalin clotting time (♀), increased alkaline phosphatase and potassium (♂), increased brain (♀) and kidney (♂) weights.
82-1b	**3-Month Feeding, Dog** Minimum Study 343-125; July 17, 1980 HED Document No. 4567 MRID No. 00127364	NOEL <250 ppm (7.25 mg/kg/day; LDT) - At this level there were signs of GI tract disturbance. 500 ppm (15 mg/kg/day) produced tremors and body weight loss in females. 750 ppm (22.25 mg/kg/day) also produced tremor, ataxia, and blood changes (↓ RBC, HCT, HGB).
82-2	**21-Day Dermal, Rabbit** Guideline Study 491-010; January 22, 1982 HED Document No. 4567 MRID No. 00127366	Systemic NOEL >3000 mg/kg/day. Local irritation only. [15 doses over 21 days]
83-1a	**Chronic Feeding, Rodent**	See 83-5
83-1b	**Chronic Feeding, Dog** Minimum Study 343-153; November 12, 1984 HED Document No. 4697 MRID No. 00143130	Systemic NOEL = 100 ppm (2.5 mg/kg/day) Systemic LEL = 250 ppm (6.25 mg/kg/day) - tremors in all dogs. Neurologic NOEL = 100 ppm (2.5 mg/kg/day)
83-2a	**Carcinogenicity, Rat**	See 83-5
83-2b	**Carcinogenicity, Mouse**	See 83-5
83-3a	**Developmental Toxicity, Rat** Guideline Study 343-216; March 13, 1990 HED Document No. 9609 MRID No. 415259-03	Maternal NOAEL = 6 mg/kg/day Maternal LEL = 10 mg/kg/day (death, moribundity, ataxia, sensitivity to external stimuli, spastic jumping, tremors, prostration, convulsions, hunched posture, squinted eyes, chromodacryorrhea, and lacrimation) Developmental NOAEL >10 mg/kg/day No developmental toxicity was observed at a dose that was lethally neurotoxic to the dams.

83-3b	**Developmental Toxicity, Rabbit** Guideline Study SMO 181/84667; November 13, 1985 HED Document No. 10114 MRID No. 00163816	Maternal NOEL = 4 mg/kg/day Maternal LEL = 12 mg/kg/day (grooming, anorexia, flicking of the forepaws) Developmental NOEL >36 mg/kg/day There were no compound-related effects on reproduction. Clinical signs: Grooming, anorexia, flicking of the forepaws and hindfeet, shaky movements, trembling, stamping of the hindfeet, lethargy.
83-4	**3-Generation Reproduction, Rat** Minimum Study SMO 164/85707; June 26, 1986 HED Document No. 10114 MRID No. 00163817	Parents (♂/♀): Systemic NOEL = 40 ppm (3.0/3.4 mg/kg/day) Systemic LEL = 120 ppm (8.9/10.1 mg/kg/day) - Body tremors with spasmodic muscle twitches, increased sensitivity and maternal lethality. Reproductive NOEL = 120 ppm (8.9/10.1 mg/kg/day) Reproductive LEL = 360 ppm (26.9/32.0 mg/kg/day) - Decreased mean F_{1B} pup weight, increased F_{2B} loss. Pups (♂/♀): Developmental NOEL = 40 ppm (3.0/3.4 mg/kg/day) Developmental LEL = 120 ppm (8.9/10.1 mg/kg/day) - Body tremors, increased mortality.
83-5	**Chronic Feeding/Carcinogenicity, Rat** Guideline Study SMO 167/851348; July 15, 1986 HED Document No. 6918 MRID No. 00163813	Systemic $NOEL_{♂}$ = 450 ppm (17.06 mg/kg/day) Systemic $NOEL_{♀}$ = 150 ppm (7.23 mg/kg/day) Systemic $LEL_{♂}$ = 600 ppm (HDT; 22.80 mg/kg/day) - Increased mortality, body tremors, increased pituitary, kidney, and adrenal weights. Systemic $LEL_{♀}$ = 450 ppm (19.45 mg/kg/day) - increased mortality and body tremors. There was no evidence of oncogenicity at any dose.

83-5	**Chronic Feeding/Carcinogenicity, Mouse** Guideline Study SMO 149/84607; December 3, 1985 HED Document No. 6918 MRID No. 00163814	Systemic NOEL >600 ppm (HDT; ♂/♀, 56.0/65.2 mg/kg/day) There were no indications of toxicity or oncogenicity other than marginally increased hyperactivity in females dosed at 600 ppm. **NOTE:** The MTD was not reached, but the study was accepted since a previous Core Supplementary study performed at the same laboratory (No. SMO 122/82228) showed a 1000 ppm dose to be lethal to 15% of the mice after only 3 weeks.
84-2a	**Gene Mutation:**	
	Ames Assay Acceptable Study FT-40-0107; March 19, 1984 HED Document No. 6918 MRID No. 00163818	Negative for *Salmonella* TA98, TA100, TA1535, TA1537, and TA1538; and *E. coli* WP2uvrA (trp$^-$) with or without metabolic activation.
84-2b	**Structural Chromosome Aberration:**	
	Sister Chromosome Exchange in CHO-K1 Cells Acceptable Study FT-40-0108; March 19, 1984 HED Document No. 6918 MRID No. 00163821	There were no increases in sister chromatid exchanges seen in the CHO-K1 cells treated with S-3206 or the DMSO vehicle.
	Cytogenetics *in vitro* (CHO/CA) Acceptable Study FT-900200; May 16, 1989 HED Document No. 010142 MRID No. 412816-01	Negative for chromosome aberrations (CA) in Chinese hamster ovary (CHO) cells exposed *in vitro* to toxic doses (≥30 ug/ml) without activation; and to limit of solubility (1000 ug/ml) with activation.
	In Vitro Assay in Mammalian Cells Acceptable Study SMO 133/8252; March 25, 1982 HED Document No. 4567 MRID No. 00126832	Equivocal results - probably of no concern.

84-2c	**Other Genotoxic Effects:**	
	DNA Damage/Repair in *Bacillus subtilis* Acceptable Study FT-00-0038; August, 1980 HED Document No. 4567 MRID No. 00126831	Not mutagenic or showing evidence of DNA damage at $\leq$5000 μg/paper disk.
85-1	**Metabolism, Rat** Acceptable Study 91-0238; June 13, 1994 HED Document No. *?* MRID No. 434768-01	Elimination was similar in both sexes. The urine:feces ratio of elimination was 1:2 following a single dose of 2.5 or 25 mg/kg, and 1:1 following 15 daily doses. The half-life was 11-16 hours in the urine, and 7-9 hours in the feces. After 7 days, >99% of the administered dose was excreted. A small percentage of radiolabel was found in the tissues (mostly in the fat). The major biotransformations included oxidation at the methyl group of the acid moiety, hydroxylation at the 4'- position of the alcohol moiety, cleavage of the ester linkage, and conjugation with sulfuric acid or glucuronic acid. The parent chemical was found in feces, but not in urine. Eight urinary metabolites and 4 fecal metabolites were identified.

85-2 **Dermal Penetration, Rat**
Acceptable
Study SC900017;
February 15, 1991
HED Document No. ?
MRID No. 434338-01

Male Sprague-Dawley (CD/BR) rats were dermally dosed with concentrations of 0.03%, 1.5%, and 30% (0.03, 1.5, and 30 mg/rat). The calculated dermal doses were 0.0013, 0.0663, and 1.26 mg/cm^2. These doses corresponded to a) the lowest concentration encountered by applicators in the field, b) the recommended field dilution, and c) the concentration found in Danitol 2.4 EC, respectively.

Mean dermal absorption between the 0.5 and 24 hour intervals was 34%, 22%, and 22% in the low, mid, and high-dose groups, respectively. Elimination was primarily in the urine, and secondarily in the feces. Absorption:elimination equilibrium was reached in as little as 4 hours at the low dose, and under 10 hours at the mid and high-doses. Elimination at the 24-hour interval for the low, mid, and high-doses was 18.2%, 8.2%, and 4.1% in the urine, and 5.8%, 1.8%, and 0.4% in the feces, respectively. The rates of elimination were 0.88%/hour, 0.38%/hour, and 0.19%/hour in the urine (between the 4 and 24 hour intervals), and 0.39%/hour, 0.13%/hour, and 0.029%/hour in the feces (between the 10 and 24 hour intervals), respectively. Residual radioactivity in the carcass was 9.0%, 3.7%, and 1.3%, respectively. Although considerable radioactivity was found in the application site skin, very little was found in the blood and non-application site skin.

Dermal absorption increased with dose concentration, but not at a proportional rate. If a recovery phase had been included in the study protocol, the total body burden could be expected to decrease rapidly upon removal of the dose in the urine and feces.

Formulation: TAME® (33.59% a.i.; contains 2.4 pounds a.i./gallon and xylene range aromatic solvent). The name of this product was changed from Danitol® 2.4 EC Spray in order to distinguish it for ornamental uses. Registration No. 59639-77.

	STUDY	RESULTS
81-1	**Acute Oral, Rat** Guideline / Toxicity Category II Study 491-003; October 26, 1981 HED Document No. 3814 MRID No. 00128341	LD_{50} = 72.5 (62.1-84.3) mg/kg, ♂ 71.8 (56.1-92.0) mg/kg, ♀ 72.1 (63.0-82.5) mg/kg, ♂+♀ **A new study is awaiting review in RD.**
81-2	**Acute Dermal, Rabbit** Minimum / Toxicity Category III Study 491-004; October 26, 1981 HED Document No. 3814 MRID No. 00128342	LD_{50} >2000 mg/kg, ♂+♀ **A new study is awaiting review in RD.**
81-3	**Acute Inhalation (1 & 4 hour), Rat** Minimum / Toxicity Category III Study 491-005; October 26, 1981 HED Document No. 3814 MRID No. 00128343	**1-hour exposure:** LC_{50} = 3.72 (3.15-4.39) mg/l, ♂ 2.75 (2.31-3.27) mg/l, ♀ 3.20 (2.86-3.58) mg/l, ♂+♀ **4-hour exposure:** LC_{50} <4.6 mg/l, ♂+♀ **A new study is awaiting review in RD.**
81-4	**Primary Eye Irritation, Rabbit** Minimum / Toxicity Category I Study WIL-194001; September 11, 1992 HED Document No. 9921 MRID No. 00429903	Corrosive to the eye.
81-5	**Primary Dermal Irritation, Rabbit** Guideline / Toxicity Category III Study 491-009; October 26, 1981 HED Document No. 3814 MRID No. 00128345	Draize score 2.2. **A new study is awaiting review in RD.**

81-6	**Dermal Sensitization, Guinea pig** Minimum Study 491-006; October 26, 1981 HED Document No. 3814 MRID No. 00128346	Two of 10 guinea pigs challenged with S-3206 2.4 EC had positive responses in a Maximization test. **NOTE:** The study report was so poorly written that it was not possible to determine how the test was performed. Considering that the technical is not a sensitizer, that the maximization test was equivocal, and that a Buehler-method test was negative, there is no reason to regard this product as a dermal sensitizer. **A new study is awaiting review in RD.**
82-2	**21-Day Dermal, Rabbit** Minimum Study 491-007; January 26, 1982 HED Document No. 3814 MRID No. 00128348	Local irritation only at 100 mg/kg/day and above. No systemic pathology at 900 mg/kg/day (HDT).

Formulation: **Danitol® 2.4 EC Spray** (33.59% a.i.)
This product is identical to TAME®, but is intended for agricultural uses.
Registration No. 59639-35

V. Action Taken to Obtain Additional Information or Clarification:

The database is complete.

VI. Reference Dose (RfD):

The RfD is 0.025 mg/kg/day. This value was derived by dividing the 1-Year Dog Feeding study NOEL of 2.5 mg/kg/day by an uncertainty factor of 100. The RfD was verified by HED on January 29, 1993, and by EPA on April 1, 1993.

VII. Pending Regulatory Actions:

There are no pending regulatory actions against the Registration of this pesticide.

VIII. Toxicologic Issues Pertinent to Granting this Request:

N/A

Compiled by John E. Whalan
Updated: October 6, 1995

Reviewed by: John E. Whalan JW 10-6-95
Section I, Tox. Branch I (H7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/23/96
Section I, Tox. Branch I (H7509C)

GUIDELINE: 85-2

DATA EVALUATION REPORT

STUDY TYPE: Dermal Absorption Study in Rats

MRID NO: 434338-01

CHEM. ID NO.: 127901

TEST MATERIALS: Danitol® 2.4EC (31.9% a.i.; amber liquid; Lot No. C82995)
^{14}C-Fenpropathrin (≥99% radiochemical purity; specific activity of 166 mCi [6.14 GBq/g]; Lot No. C-89-049)

SYNONYMS: Danitol®

STUDY NUMBER(S): Battelle SC900017

SUBMITTED BY: Valent U.S.A. Corporation

TESTING FACILITY: Battelle Columbus Division, Columbus, Ohio

TITLE OF REPORT: Dermal Absorption of ^{14}C-Fenpropathrin in DANITOL® Using Male Sprague-Dawley Rats.

AUTHOR(S): Jerry D. Johnson, Craig R. Mahon, and Joanne M. Killinger

REPORT ISSUED: February 15, 1991

SUMMARY: Dermal penetration and excretion of radiolabelled fenpropathrin was measured following single administrations in male Sprague-Dawley (CD/BR) rats. Groups of thirty rats were randomly assigned to three dose levels — 0.03% (lowest concentration encountered by applicators in the field), 1.5% (recommended field dilution), and 30% (concentration found in Danitol 2.4 EC). The corresponding doses were 0.03, 1.5, and 30 mg/rat (calculated doses were 0.0013, 0.0663, and 1.26 mg/cm^2). Within each of the three dose levels were 6 termination groups of 5 rats each which were sequentially sacrificed at intervals of 0.5, 1, 2, 4, 10, and 24 hours.

Mean dermal absorption between the 0.5 and 24 hour intervals was 34%, 22%, and 22% in the low, mid, and high-dose groups, respectively. Elimination was primarily through the urine, and secondarily through the feces. Absorption:elimination equilibrium was reached in as little as 4 hours at the low dose, and under 10 hours at the mid and high-doses. Elimination at the 24-hour

interval for the low, mid, and high-doses was 18.2%, 8.2%, and 4.1% in the urine, and 5.8%, 1.8%, and 0.4% in the feces, respectively. The rates of elimination for the low, mid, and high concentrations were 0.88%/hour, 0.38%/hour, and 0.19%/hour in the urine (between the 4 and 24 hour intervals), and 0.39%/hour, 0.13%/hour, and 0.029%/hour in the feces (between the 10 and 24 hour intervals), respectively. Residual radioactivity in the carcass was 9.0%, 3.7%, and 1.3%, respectively. Although considerable radioactivity was found in the application site skin, very little was found in the blood and non-application site skin. Group mean radioactivity recovery for any given dose/interval group ranged from 96.8% to 110.8%.

Dermal absorption increased with dose concentration, but not at a proportional rate. The percentage of dose absorbed decreased as dose concentration increased. That is why the percentage of dose found in the urine, feces, blood, carcass, and application site skin was greatest in the low-dose group and least in the high-dose group. If a recovery phase had been included in the study protocol, the total body burden could be expected to decrease rapidly upon removal of the dose in the urine and feces.

STUDY CLASSIFICATION: This study is **Acceptable**, and satisfies data requirement 85-3 for a Dermal Absorption study. Study room temperature dropped to 65°C on one day, which was below the protocol limits of 67-77°C. This should not adversely affected the study's outcome. Although the rat's CO_2 was measured for radioactivity, there was no mention of the findings. Considering that virtually all of the radioactivity was accounted for, this is not a concern. This study received Quality Assurance review.

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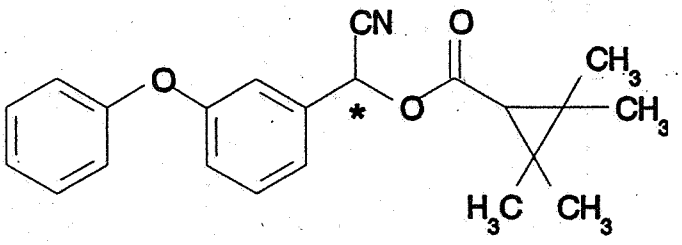
PROTOCOL: Dermal penetration and excretion of radiolabelled fenpropathrin was measured following single administrations in male Sprague-Dawley (CD/BR) rats. The radiolabelled test article was dissolved in a 1:1 mixture of toluene and hexane and stored at approximately 4°C. Unlabelled Danitol was stored at room temperature.



* Position of the ^{14}C-radiolabel.

A stream of nitrogen gas was used to remove the toluene:hexane solvent from the radiolabelled fenpropathrin. Blank Danitol® 2.4 EC (i.e. Danitol 2.4 EC without the active ingredient) and distilled water were used to prepare the formulations. All formulations were prepared within a day of the first dosing and used for no more than 4 days. They were evaluated for stability, homogeneity, and dose concentration.

Prior to the main study, experiments were performed to assess the extent of volatility of ^{14}C-fenpropathrin and the total percent of recovery. Following a one week quarantine period, the male rats selected for the main study were approximately 7-9 weeks old and weighed 237-282 g. They were housed in polycarbonate metabolism cages for the collection of elimination products. Certified Purina Rodent Chow® and water were available *ad libitum*.

Groups of thirty rats were randomly assigned to three dose levels. Within each dose level there were 6 termination groups of 5 rats each which were sequentially sacrificed at intervals of 0.5, 1, 2, 4, 10, and 24 hours. The target doses were as follows:

			Target Concentration		
Formulation (% a.i.)	**Dermal Dose (mg/cm^2)**	**Dermal Dose (mg/rat)**	**mg/ml**	**µCi/ml**	**GBq/ml**
0.03%[1]	0.00125	0.03	0.3	50	1.85x10-3
1.5%[2]	0.0625	1.5	15	150	5.55x10-3
30%[3]	1.25	30	300	150	5.55x10-3

[1] Lowest concentration encountered by applicators in the field.
[2] Recommended field dilution.
[3] Concentration found in Danitol 2.4 EC

The day before dosing, the application sites were clipped and wiped with acetone to remove skin oil and debris. Rats with abraded skin were replaced. On the day of dosing, each rat was weighed, then dermally dosed via a positive displacement pipette with a 100 µl aliquot of ^{14}C-fenpropathrin on a 4 x 6 cm area of skin over a 5 minute period. The rats were manually restrained for 5-10 minutes so the dose could air dry. The application site was covered with a non-occlusive protective appliance (Reston® foam spacer covered with wire mesh screen and filter paper) secured with Elastikon® adhesive bandage, and left in place until termination. Each rat was placed into a metabolism cage immediately after dosing.

At termination, the protective appliance was removed, the application site was washed with Ivory® soap and water and dried (using Q-Tips®), a sample of cardiac blood was drawn and heparinized, and the application site, with bordering skin and untreated areas of skin, were removed from the carcass. Urine and feces were collected for each rat, and the metabolism cages were washed with methanol and deionized water. The volumes of urine and cage rinses, and fecal weights were recorded. Tissues and carcasses were weighed, and carcasses were homogenized. Samples were stored at -20°C. ^{14}C-fenpropathrin measurements were made of the skin samples, residual carcass, application site skin washes, protective appliance extracts, urine, feces, and cage rinses.

^{14}C-fenpropathrin was measured in duplicate by sample combustion and/or liquid scintillation counting. The dosing formulations were analyzed in triplicate whenever possible. A Packard Sample Oxidizer (Model 306) was used to combust all fecal, skin, carcass, and blood samples. The released $^{14}CO_2$ was trapped in Carbo-Sorb® and mixed with Permafluor®. A Beckman LS 7800 Scintillation Counter was used to measure ^{14}C-radioactivity. Instrument performance standards were evaluated between every 10 study samples to assure accuracy and consistency.

RESULTS:

Test Article: The ^{14}C-fenpropathrin used in this study was compared to reference standards and found to have a chemical purity of >99% and a radiochemical purity of >99%. Measurements of the high-concentration showed that the refrigerated test article was stable and homogeneous over a period of 5 days. Dose concentrations remained within ±6.3% of nominal, and dose variation from animal-to-animal was slight.

Radioactive residue on the protective appliance was <3% for all but one group. The high-dose group which was dosed for 24 hours had 6% retention due to the migration of an oily formulation over a long period of time. The calculated doses for the 0.03%, 1.5%, and 30% concentrations were 0.0013, 0.0663, and 1.26 mg/cm^2, respectively.

Dosing Site:

Group Mean Percentage of Dose in the Skin Washes (S.D.)

Termination Period (Hrs.)	0.03%	1.5%	30.0%
0.5	89.1 (4.6)	95.7 (3.0)	99.6 (6.5)
1	81.0 (4.6)	90.3 (6.1)	100.8 (1.6)
2	83.1 (3.0)	87.7 (6.2)	98.7 (7.3)
4	75.2 (10.7)	84.2 (3.3)	93.3 (3.3)
10	68.9 (2.9)	80.6 (11.2)	88.8 (4.5)
24	54.7 (5.2)	74.2 (5.8)	77.3 (4.5)

Dermal absorption (i.e. the percentage of chemical not removed by washing) gradually increased with time. Between the 0.5 and 24 hour intervals, mean dermal absorption was 34%, 22%, and 22% in the low, mid, and high-dose groups, respectively.

Urinary Elimination:

Group Mean Percentage of Dose Excreted in the Urine (S.D.)

Termination Period (Hrs.)	0.03%	1.5%	30.0%
0.5	0.0 (0.1)	0.0 (0.0)	0.0[a]
1	0.1 (0.1)	0.0 (0.1)	0.0 (0.0)
2	0.4 (0.0)	0.2 (0.0)	0.1 (0.1)
4	0.7 (0.4)	0.6 (0.2)	0.3 (0.1)
10	5.3 (1.1)	2.5 (0.7)	1.2 (0.3)
24	18.2 (5.4)	8.2 (1.6)	4.1 (0.6)

[a] This value is for only one animal because the other animals in the group either did not urinate, or their urine was below the detection limit.

Figure 5 (p57) from the study report (attached) graphically portrays urinary elimination over 24 hours. This graph is misleading because the x-axis (time) is not linear. When corrected for linearity, elimination after the 4-hour interval yields straight lines for each of the three groups. After 4 hours, all three groups had eliminated less than 1% of their doses in their urine. After 24 hours, urinary elimination was 18.2%, 8.2%, and 4.1% in the low, mid, and high-dose groups. Percent urinary excretion decreased as the dose increased, probably due to a combination of a decreased dermal absorption rate and saturation of elimination pathways as dosage increased.

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____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

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Fecal (Biliary) Elimination:

Group Mean Percentage of Dose Excreted in the Feces (S.D.)

Termination Period (Hrs.)	0.03%	1.5%	30.0%
0.5	BDL[a]	BDL	BDL
1	BDL	BDL	BDL
2	BDL	0.0[b]	0.0[b]
4	BDL	0.0[b]	BDL
10	0.4 (0.3)	0.0 (0.1)	0.0 (0.0)
24	5.8 (2.6)	1.8 (0.3)	0.4 (0.2)

[a] Below detection limits (BDL)
[b] This value is for one or two animals because the other animals' values were below detection limits.

These data show biliary elimination to be a less significant elimination route than the urine. Virtually no radioactivity was found in the feces until the 10-hour interval. At some point after 10 hours, the recovery of radioactivity sharply increased. This is graphically portrayed in Figure 7 (p61, attached) from the study report. This graph, like Figure 5, is misleading because the x-axis (time) is not linear. As was seen in the urine, the percentage of fecal excretion decreased as the dose increased. This was probably due to a combination of a decreased rate of dermal absorption and saturation of elimination pathways as dosage increased.

Total Percent Recovery:

Group mean recovery for any given dose/interval group ranged from 96.8% to 110.8%. The mean recovery for the low, mid, and high-dose groups (intervals combined) was 104%, 101%, and 107%, respectively. A table detailing distribution and total recovery for each of the sacrifice intervals is attached at the end of this review.

DISCUSSION: There was no mention of radioactivity in the captured CO_2, presumably because none was found. The level of radioactivity found in the application site skin, which was considerable at every termination interval, increased at a gradual rate with exposure due to slow absorption. Dermal absorption increased as dose concentration increased, but not at a proportional rate. That is why the percentage of dose found in the urine, feces, blood, carcass, and application site skin was greatest in the low-dose group and least in the high-dose group.

As would be expected, the percentage of dose found in various tissues and elimination products increased with time of exposure. Total body burden reached a plateau in each dose group; that is the rate of elimination approximately equalled the rate of dermal absorption. This equilibrium

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____ Identity of the source of product ingredients.

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____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

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was reached after 4 hours in the low-dose group (27.1% of dose), and after 10 hours in the mid and high-dose groups (17.6% and 16.4% of dose, respectively). These data suggest that if a recovery phase had been included, the total body burden could be expected to decrease rapidly through excretion into the urine and feces.

Thus, it appears that fenpropathrin is readily absorbed through the skin of the rat, that elimination is primarily through the urine, and secondarily through the feces, and that equilibrium is reached in as little as 4 hours at low doses (0.03%), and no more than 10 hours at higher doses (1.5% and 30%). The rates of elimination for the low, mid, and high concentrations were 0.88%/hour, 0.38%/hour, and 0.19%/hour in the urine (between the 4 and 24 hour intervals), and 0.39%/hour, 0.13%/hour, and 0.029%/hour in the feces (between the 10 and 24 hour intervals), respectively.

Dose Distribution Following a Single Dermal Dose in Rats

Interval	Protective Appliance	Skin Wash	Dosed Skin	Blood		Carcass	Urine	Feces	Absorbed[a]		Total
hours	%	%	%	%	µg/cm²	%	%	%	%	µg/cm²	%
				0.03% (0.0013 mg/cm²)[b]							
0.5	1.6	89.1	14.6	0.3	0.006	2.3	<0.05	BDL	2.6	0.03	107.9
1	0.2	81.0	15.2	0.1	0.003	1.2	0.1	BDL	2.4	0.03	97.8
2	0.2	83.1	17.2	0.3	0.007	2.4	0.4	BDL	3.1	0.04	103.6
4	0.3	75.2	24.7	0.2	0.004	2.2	0.7	BDL	3.1	0.04	103.3
10	1.1	68.9	19.9	0.5	0.010	7.1	5.3	0.4	13.3	0.17	103.2
24	1.3	54.7	21.1	0.4	0.007	9.0	18.2	5.8	33.4	0.43	110.5
				1.5% (0.0663 mg/cm²)[b]							
0.5	0.1	95.7	8.5	0.1	0.06	0.3	<0.05	BDL	0.4	0.27	104.7
1	0.3	90.3	10.2	0.1	0.11	0.6	<0.05	BDL	0.7	0.46	99.9
2	0.1	87.7	11.8	0.2	0.16	0.8	0.2	0.0	1.2	0.80	100.4
4	0.5	84.2	11.2	0.2	0.18	1.3	0.6	0.0	2.1	1.39	98.0
10	0.3	80.6	14.7	0.2	0.22	2.7	2.5	0.0	5.4	3.58	103.5
24	0.4	74.2	15.0	0.2	0.22	3.7	8.2	1.8	13.9	9.22	103.5
				30.0% (1.26 mg/cm²)[b]							
0.5	0.9	99.6	9.0	<0.05	0.57	BDL	<0.05	BDL	<0.05	<0.63	109.5
1	0.8	100.8	6.7	<0.05	0.77	BDL	<0.05	BDL	<0.05	<0.63	108.3
2	0.8	98.7	9.0	0.1	1.90	0.5	0.1	0.0	0.7	8.82	109.2
4	3.1	93.3	11.4	0.1	2.32	0.6	0.3	BDL	1.0	12.60	108.8
10	1.7	88.8	15.3	0.1	2.36	1.0	1.2	0.0	2.3	28.98	108.8
24	6.1	77.3	11.6	0.1	1.59	1.3	4.1	0.4	5.9	74.34	100.9

[a] - Sum of blood, carcass, urine, and feces.
[b] - Measured dose.
BDL - Below Detectable Limits.
NOTE: The values for each dose interval are for 5 male rats each.

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Reviewed by: John E. Whalan JW 8-29-95
Section I, Tox. Branch I (H7509C)
Secondary reviewer: Roger L. Gardner Roger Gardner 1/23/96
Section I, Tox. Branch I (H7509C)

GUIDELINE: 85-1

DATA EVALUATION REPORT

STUDY TYPE: Metabolism Study in Rats

MRID NO: 434768-01

CHEM. ID NO.: 127901

TEST MATERIALS: a. ^{12}C-S-3206 (unlabelled fenpropathrin; 99.9% a.i.; Lot No. 10618S)
b. [Alcohol-^{14}C]-S-3206 (98.7% a.i.; Lot No. C-91-089)
c. [Acid-^{14}C]-S-3206 (98.5% a.i.; Lot No. C-90-039)

SYNONYMS: Danitol®

STUDY NUMBER(S): Battelle 91-0238 (3993-91-0238-AM-002)

SUBMITTED BY: Valent U.S.A. Corporation

TESTING FACILITY: Ricerca, Inc., Department of Toxicology and Animal Metabolism

TITLE OF REPORT: Excretion, Distribution and Metabolism of [^{14}C]S-3206 Following Single or Multiple Dose Administration to Rats.

AUTHOR(S): M.C. Savides, T.P. Green, D.B. Johnson, and J. Laveglia

REPORT ISSUED: June 13, 1994

SUMMARY: Groups of 5 male and 5 female Crl:CD®BR® VAF/Plus (Sprague-Dawley) rats were dosed with radiolabelled S-3206 (fenpropathrin) by three protocols. They were dosed with S-3206 radiolabelled on either the alcohol or acid portion of the molecule (i.e. [alcohol-^{14}C]-S-3206 or [acid-^{14}C]-S-3206). In Experiment I, rats received 14 daily oral low-doses of 2.5 mg/kg/day of unlabelled S-3206 followed by a 15th dose of either the alcohol or acid radiolabelled S-3206. In Experiments II and III, groups of rats received a single dose of either of the two radiolabelled test articles at 2.5 mg/kg (II) or 25 mg/kg (III). No clinical signs were seen in any rats.

Elimination for both sexes was similar in the single low and high-dose experiments (II and III), with about one-third of the dose being eliminated in the urine (II - 30-40%; III - 28-35%) and the balance in the feces (II and III - 65-69%). In the multiple dose experiment (I), half of the elimination was in the urine (52-56%) and the remainder in the feces (46-55%) for both sexes.

The half-life was 11-16 hours in the urine, and 7-9 hours in the feces. In all three experiments, >99% of the administered dose was excreted after 168 hours (7 days). The small percentage of radiolabel found in the tissues was mostly in the fat.

The major biotransformations included oxidation at the methyl group of the acid moiety, hydroxylation at the 4'- position of the alcohol moiety, cleavage of the ester linkage, and conjugation with sulfuric acid or glucuronic acid.

Four metabolites were found and characterized in the urine of rats dosed with alcohol-radiolabel. The major metabolites were the sulfate conjugate of 3-(4'-hydroxyphenoxy)benzoic acid and 3-phenoxybenzoic acid (22-44% and 3-9% of the administered dose, respectively). Eight metabolites were found in the urine of rats dosed with acid-radiolabel, but only 4 were characterized. The major urinary metabolites of the acid-labeled fenpropathrin were TMPA-glucuronic acid and TMPA-CH_2OH (11-26% and 6-10% of the administered dose, respectively). None of the parent chemical was found in urine.

The major elimination products in the feces included the parent chemical (13-34% of the administered dose) and 4 metabolites. The fecal metabolites (and the percentage of administered dose) included CH_2OH-fenpropathrin (9-20%), 4'-OH-fenpropathrin (4-11%), COOH-fenpropathrin (2-7%), and 4'-OH-CH_2OH-fenpropathrin (2-7%).

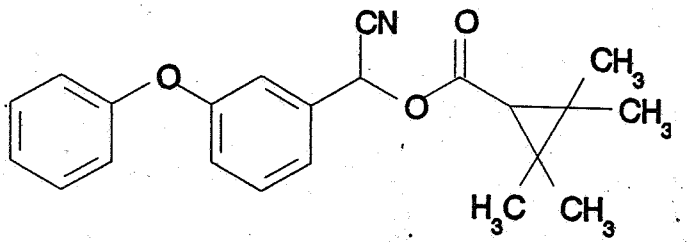
STUDY CLASSIFICATION: This study is **Acceptable**, and satisfies data requirement 85-1 for a Metabolism study. This study received Quality Assurance review. The NMR analyses of five metabolites were performed at a laboratory that lacks a GLP program. The laboratory that performed high resolution mass spectral analyses has a GLP program, but their study report did not mention GLP compliance. There was no evidence of these deficiencies affecting the outcome of the study.

****

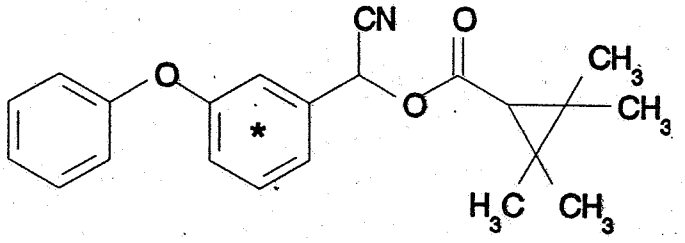
PROTOCOL: The test system used in this study was Crl:CD®BR® VAF/Plus (Sprague-Dawley) rats, a commonly used strain in metabolism studies. At the time of dosing, the rats were 5-6 weeks old, and weighed 215-315 g for males, and 161-212 g for females. A total of 30 males and 30 females were dosed, and another 6 males and 6 females served as control animals. The controls were used solely to supply tissues for background radioactivity levels. The rats were individually housed in stainless steel cages. Following dosing with the radiolabelled test article, they were transferred to Nalgene® metabolism cages for the collecting of urine and feces. Food and water were available *ad libitum*.

The three test articles included unlabelled S-3206 (fenpropathrin), and S-3206 radiolabelled in the alcohol and acid positions. The nonradiolabelled S-3206 was characterized by mass spectroscopy, and the purity was measured by HPLC and TLC. The radiolabelled test articles were characterized by mass spectroscopy and the radiochemical purities were determined by HPLC and TLC with radiochemical detection.

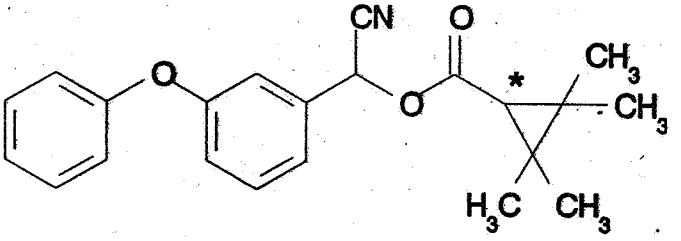
^{12}C-S-3206 (unlabelled fenpropathrin)



[Alcohol-^{14}C]-S-3206:



[Acid-^{14}C]-S-3206:



* Position of the ^{14}C-radiolabel.

Although all metabolites were isolated at Ricercá, this laboratory lacked the necessary instrumentation for analysis. Rutgers University (a GLP laboratory) performed high resolution mass spectroscopy, and the University of Akron (which lacks a GLP program) performed NMR analyses. The dosing regimens are described in the following table:

Table 1. Dosing Regimens

Experiment	Number/Sex	Compound	Dose Level	Duration
I A	5/sex	[^{12}C]S-3206 [Alcohol-^{14}C]-S-3206	2.5 mg/kg/day for 14 days 2.5 mg/kg on day 15	7 days after day 15
I B	5/sex	[^{12}C]S-3206 [Acid-^{14}C]-S-3206	2.5 mg/kg/day for 14 days 2.5 mg/kg on day 15	7 days after day 15
I C	1/sex/label*	Vehicle (corn oil)	0 mg/kg/day for 15 days	7 days after day 15
II A	5/sex	[Alcohol-^{14}C]-S-3206	2.5 mg/kg/day	7 days
II B	5/sex	[Acid-^{14}C]-S-3206	2.5 mg/kg/day	7 days
II C	1/sex/label*	Vehicle (corn oil)	0 mg/kg/day	7 days
III A	5/sex	[Alcohol-^{14}C]-S-3206	25 mg/kg/day	7 days
III B	5/sex	[Acid-^{14}C]-S-3206	25 mg/kg/day	7 days
III C	1/sex/label*	Vehicle (corn oil)	0 mg/kg/day	7 days

* One male and one female served as controls for each of the two radiolabelled test articles.

All rats were dosed with a volume of approximately 5 ml/kg body weight. The three experiments were designed to determine the elimination and distribution of radiolabel, and the identity and quantity of metabolites.

In experiment I, rats were given 14 consecutive daily doses of nonradiolabelled S-3206 at the low-dose of 2.5 mg/kg/day. Twenty-four hours after the 14th dose, they were given an equivalent dose of either the alcohol or acid radiolabelled test article. The rats were terminated 168 hours (7 days) after the radiolabelled dose.

In experiment II, rats were given a single low-dose of either the alcohol or acid radiolabelled test article. The rats were terminated 168 hours (7 days) later. Experiment III resembled experiment II except that the rats received a single high-dose of 25 mg/kg.

Nonradiolabelled S-3206 was dissolved in Mazola® corn oil to achieve a nominal concentration of 0.5 mg/ml. Radiolabelled doses were prepared by dissolving radiolabelled and nonradiolabelled test articles in acetone. The solvent was evaporated in a gentle stream of nitrogen gas, and then the test articles were added to corn oil to achieve nominal concentrations of 0.5 mg/ml and 5 mg/ml, which were intended for the 2.5 and 25 mg/kg doses, respectively. Solutions were analyzed for dose concentration, radioconcentration, stability, and chemical and radiochemical purity. The rats were orally dosed by intubation needle. The controls were dosed with corn oil. The actual dose administered was measured by weighing the syringes before and after dosing.

The study report cites a 1977 metabolism publication and a Sumitomo Chemical Company Report (not otherwise specified) as justification for not measuring radiolabel in expired CO_2. Urine was collected 12 and 24 hours after radiolabel dose administration, and every 24 hours thereafter. Urine was collected over dry ice, then stored at -6°C. Feces were collected at 24-hour intervals.

Samples were weighed, then frozen for storage. The urine/feces separator of each metabolism cage was rinsed with HPLC-grade water and HPLC-grade methanol. Radioactivity found in the rinse was attributed to the urine.

At termination, the rats were anesthetized and exsanguinated. Blood was collected in heparinized tubes and refrigerated. Harvested tissues include heart, lungs, spleen, liver, kidneys, gonads, brain, femur, hind-leg muscle (semimembranosus), mesenteric fat, and the residual carcass. These samples were stored at -6°C. The carcass was cut into small pieces, then homogenized in a Hobart® grinder. Large tissues were minced with scissors, and small tissues (spleen, ovaries, and bone) were bisected. Fecal samples were homogenized with dry ice in a Waring® blender.

Urine and fecal extracts were analyzed by HPLC with radioactivity detection (HPLC/RAD) and/or HPLC with subsequent liquid scintillation counting (HPLC/LSC). Urine, plasma, and cage wash samples were measured directly, but whole blood, feces, and tissue samples were analyzed following combustion of duplicate aliquots by biological oxidation. Three HPLC solvent systems were used to isolate metabolites for NMR spectroscopic analyses.

Metabolite identification during Experiments II and III was limited to those metabolites identified during Experiment I. Urine for metabolite identification was collected at 0-12, 12-24, and 24-48 hours for 2 rats/sex from each radiolabel group in Experiment I.

RESULTS: The dosing solutions were stable and homogeneous, and had an average purity of 99%. The mean administered doses in the three experiments were as follows:

Experiment I - Mean Administered Dose (S.D.)

Experimental Group	Sex	mg of S-3206/kg	μCi Administered
IA (alcohol-)	Males	2.5 (0.0)	67.6 (8.8)
	Females	2.5 (0.1)	44.0 (3.4)
IB (acid-)	Males	2.6 (0.0)	46.5 (1.7)
	Females	2.5 (0.0)	31.4 (2.6)

Experiment II - Mean Administered Dose (S.D.)

Experimental Group	Sex	mg of S-3206/kg	μCi Administered
IIA (alcohol-)	Males	2.4 (0.0)	52.6 (1.2)
	Females	2.5 (0.0)	47.0 (2.2)
IIB (acid-)	Males	2.6 (0.0)	47.6 (3.2)
	Females	2.6 (0.0)	35.9 (1.8)

Experiment III - Mean Administered Dose (S.D.)

Experimental Group	Sex	mg of S-3206/kg	μCi Administered
IIIA (alcohol-)	Males	24.3 (0.3)	66.7 (0.3)
	Females	24.8 (0.3)	54.6 (2.6)
IIIB (acid-)	Males	26.2 (1.3)	43.5 (1.5)
	Females	25.8 (0.2)	36.0 (1.4)

Experiment I - Multiple Low-Dose: After 14 days of NOEL dosing (2.5 mg/kg/day) with unlabelled S-3206, the rats were dosed with 2.5 mg/kg of either [alcohol-^{14}C]-S-3206 or [acid-^{14}C]-S-3206. No clinical signs were observed in any rats. The mean percentages of dose found in the urine, feces, and tissues, and rates of excretion are presented below:

Experiment I - Mean Percentage Excretion of Radiolabelled Dose (S.D.)

Dose/Label/Sex	Urine	Feces	Tissues	Total Recovery
Low-dose/alcohol/male	52.30 (8.37)	54.66 (9.18)	0.97 (0.35)	107.93 (2.26)
Low-dose/alcohol/female	55.39 (4.80)	51.14 (4.21)	0.71 (0.34)	107.24 (2.95)
Low-dose/acid/male	51.85 (5.35)	51.89 (3.70)	1.26 (0.19)	105.01 (3.06)
Low-dose/acid/female	56.47 (7.76)	46.47 (6.03)	0.77 (0.09)	103.70 (2.91)

Experiment I - Mean Percentage Excretion of Radiolabelled Dose (by Hours)

Dose/Label/Sex	12	24	48	72	96	120	144	168	Total Recovery
Urine									
Low-dose/alcohol/male	31.42	15.27	3.55	0.88	0.47	0.32	0.23	0.16	52.30
Low-dose/alcohol/female	36.51	13.35	3.52	0.91	0.52	0.28	0.17	0.12	55.39
Low-dose/acid/male	26.13	18.43	5.13	1.07	0.49	0.29	0.18	0.13	51.85
Low-dose/acid/female	36.50	14.41	3.91	0.81	0.37	0.22	0.15	0.10	56.47
Feces									
Low-dose/alcohol/male	—	42.27	10.63	0.96	0.31	0.23	0.14	0.11	54.66
Low-dose/alcohol/female	—	43.49	6.46	0.58	0.27	0.16	0.11	0.07	51.14
Low-dose/acid/male	—	38.98	10.72	1.08	0.38	0.54	0.11	0.08	51.89
Low-dose/acid/female	—	38.05	7.25	0.63	0.25	0.14	0.09	0.07	46.47

These data show that in rats dosed over 15 consecutive days, both sexes eliminate the alcohol and acid similarly, with about half of the dose being eliminated in the urine and the remainder in the feces. Urinary elimination peaked at 12 hours (26-37% of dose), and the urinary half-life was 11-13 hours. Fecal elimination peaked at 24 hours (38-43% of dose), and the fecal half-life was 8-9 hours. After 72 hours, more than 98% of the urinary and fecal elimination had occurred. Only

about 1% of the radiolabel could be found in the tissues, predominately in the fat (0.16-0.31 μg equivalents/gram). No radiolabel was found in the heart, lung, spleen, kidney, gonads, and brain, and only traces were found in the blood, liver, muscle, bone, and carcass. Once dosing ceased, ≥99% of the dose was eliminated over the course of 7 days.

Experiment II - Single Low-Dose: Rats were given a single 2.5 mg/kg/day dose of either [alcohol-^{14}C]-S-3206 or [acid-^{14}C]-S-3206. No clinical signs were observed in any rats. The mean percentages of dose found in the urine, feces, and tissues, and rates of excretion are presented below:

Experiment II - Mean Percentage Excretion of Radiolabelled Dose (S.D.)

Dose/Label/Sex	Urine	Feces	Tissues	Total Recovery
Low-dose/alcohol/male	35.97 (6.49)	69.03 (4.72)	0.47 (0.24)	105.47 (2.54)
Low-dose/alcohol/female	39.74 (6.25)	64.95 (3.66)	0.25 (0.04)	104.94 (2.86)
Low-dose/acid/male	29.87 (4.13)	68.39 (5.34)	0.67 (0.18)	98.93 (2.21)
Low-dose/acid/female	34.24 (9.12)	64.68 (5.85)	0.52 (0.08)	99.43 (3.62)

Experiment II - Mean Percentage Excretion of Radiolabelled Dose (by Hours)

Dose/Label/Sex	12	24	48	72	96	120	144	168	Total Recovery
Urine									
Low-dose/alcohol/male	16.17	15.55	2.98	0.57	0.30	0.17	0.12	0.10	35.97
Low-dose/alcohol/female	17.94	16.14	4.43	0.63	0.28	0.15	0.09	0.07	39.74
Low-dose/acid/male	12.79	9.99	5.31	0.92	0.40	0.23	0.13	0.11	29.87
Low-dose/acid/female	17.57	10.56	4.36	0.92	0.38	0.20	0.13	0.11	34.24
Feces									
Low-dose/alcohol/male	—	58.72	9.07	0.64	0.26	0.15	0.11	0.07	69.03
Low-dose/alcohol/female	—	56.22	7.89	0.40	0.21	0.11	0.08	0.05	64.95
Low-dose/acid/male	—	58.44	8.47	0.87	0.31	0.14	0.09	0.06	68.39
Low-dose/acid/female	—	54.28	8.56	1.30	0.30	0.11	0.07	0.05	64.68

Both sexes eliminated the alcohol and acid similarly after receiving a single dose of 2.5 mg/kg. About a third of the dose was eliminated in the urine, with the balance in the feces. Less than 1% of the dose was found in the tissues.

Urinary elimination was similar at 12 and 24 hours (10-18% of dose), and the urinary half-life was 12-16 hours. Fecal elimination peaked at 24 hours (54-59% of dose), and the fecal half-life was 7-9 hours. After 72 hours, more than 99% of the urinary and fecal elimination had occurred. Less than 0.7% of the radiolabel could be found in the tissues, predominately in the fat (mean of 0.1 μg equivalents/gram). No radiolabel was found in the heart, lung, spleen, gonads, and

brain, and only traces were found in the blood, kidney, liver, muscle, bone, and carcass. Seven days after a single low-dosing, ≥99% of the dose had been eliminated.

Experiment III - Single High-Dose: Rats were given a single 25 mg/kg/day dose of either [alcohol-^{14}C]-S-3206 or [acid-^{14}C]-S-3206. No clinical signs were observed. The mean percentages of dose found in the urine, feces, and tissues, and rates of excretion are presented below:

Experiment III - Mean Percentage Excretion of Radiolabelled Dose (S.D.)

Dose/Label/Sex	Urine	Feces	Tissues	Total Recovery
High-dose/alcohol/male	31.86 (3.89)	65.25 (4.10)	0.31 (0.07)	97.41 (2.08)
High-dose/alcohol/female	27.85 (4.33)	65.14 (5.22)	0.27 (0.06)	93.26 (4.79)
High-dose/acid/male	32.04 (8.51)	68.60 (10.36)	0.52 (0.11)	101.16 (3.68)
High-dose/acid/female	35.37 (11.26)	64.99 (9.66)	0.42 (0.13)	100.78 (3.67)

Experiment III - Mean Percentage Excretion of Radiolabelled Dose (by Hours)

Dose/Label/Sex	12	24	48	72	96	120	144	168	Total Recovery
Urine									
High-dose/alcohol/male	14.25	13.80	2.63	0.63	0.25	0.15	0.09	0.08	31.86
High-dose/alcohol/female	10.31	12.59	3.82	0.59	0.24	0.14	0.09	0.08	27.85
High-dose/acid/male	11.61	13.67	4.96	0.96	0.38	0.22	0.14	0.09	32.04
High-dose/acid/female	12.74	13.98	6.92	0.94	0.36	0.20	0.15	0.09	35.37
Feces									
High-dose/alcohol/male	—	58.69	4.97	1.06	0.26	0.13	0.08	0.05	65.25
High-dose/alcohol/female	—	53.38	10.72	0.63	0.20	0.10	0.06	0.05	65.14
High-dose/acid/male	—	59.82	7.15	1.09	0.27	0.13	0.08	0.06	68.60
High-dose/acid/female	—	52.53	10.69	1.32	0.23	0.10	0.06	0.06	64.99

Both sexes of rats which received a single dose of 25 mg/kg eliminated the alcohol and acid similarly. About a third of the dose was eliminated in the urine, with the balance in the feces. Less than 1% of the dose was found in the tissues.

Urinary elimination was similar at 12 and 24 hours (10-14% of dose), and the urinary half-life was 13-16 hours. Fecal elimination peaked at 24 hours (53-60% of dose), and the fecal half-life was 7-9 hours. After 72 hours, more than 99% of the urinary and fecal elimination had occurred. Less than 0.5% of the radiolabel was found in the tissues, predominately in the fat (mean of 1.0 μg equivalents/gram). No radiolabel was found in the heart, lung, spleen, gonads, and brain, and only traces were found in the blood, kidney, liver, muscle, bone, and carcass. Seven days after a single high-dosing, ≥99% of the dose had been eliminated. Aside from a 10-fold increase in retained radiolabel in the fat, the elimination of the high-dose resembled that in the low dose.

Urinary Metabolite Identification: Experiments I, II, and III demonstrated that similar percentages of alcohol and acid radiolabel were eliminated in the urine, but the difference in metabolic profiles for the two radiolabels suggest that the fenpropathrin molecule is cleaved at the ester linkage between the cyclopropyl and aromatic moieties.

The metabolic profiles were similar for both sexes. Four metabolites were identified in the urine of rats treated with alcohol-labelled fenpropathrin. Eight metabolites were found in the urine of rats treated with acid-labelled fenpropathrin, but only 4 of these could be identified.

Urinary Metabolites - Alcohol-Radiolabel

Metabolite	% of Administered Dose	% in Urine
4'-OH-PBacid sulfate[1]	22.0-44.2	78.3-82.8
4'-OH-PBacid[2]	0.8-2.1	1.7-5.5
PBacid[3]	3.0-9.2	10.0-18.4
3-PHacid[4]	0.3-1.7	0.9-3.1

[1] sulfate conjugate of 3-(4'-hydroxyphenoxy)benzoic acid
[2] 3-(4'-hydroxyphenoxy)benzoic acid
[3] 3-phenoxybenzoic acid
[4] 3-phenoxyhippuric acid (the glycine conjugate of PBacid)

Urinary Metabolites - Acid-Radiolabel

Metabolite	% of Administered Dose	% in Urine
Zone 1	1.2-3.1	3.0-6.7
Zone 2	0.8-9.4	2.4-19.0
TMPA-CH_2OH (Zone 3)	6.0-10.1	11.0-34.5
TMPA-COOH (trans)	0-5.3	0-9.6
Zone 4	0-6.9	0-12.6
Zone 5[1]	0-2.0	0-6.0
TMPA-$(CH_2OH)_2$-lactone	0-1.6	0-4.1
TMPA-glucuronic acid[2]	10.5-25.8	35.0-47.2
Zone 6[1]	2.0-5.7	5.9-17.6

[1] These metabolites were found in Experiments II and III (single dose protocols), but not in Experiment I (multiple dose).
[2] 2,2,3,3,-tetramethylcyclopropanecarboxylic acid

The major urinary metabolites of the acid-labeled fenpropathrin were TMPA-glucuronic acid (10.5-25.8%) and TMPA-CH_2OH (6.0-10.1%). A considerable percentage of the zone 2 metabolite was found in Experiment I after multiple dosings (7.5-9.4% of the administered dose), but very little was found following single doses in Experiments II and III (about 1%).

Fecal Metabolite Identification: Four metabolites were identified in the feces of rats treated with alcohol and acid-labelled fenpropathrin. The metabolic profiles were similar for both sexes whether treated with the alcohol or acid radiolabel. Most radioactivity was due to unmetabolized fenpropathrin. The fecal metabolites are as follows:

Fecal Metabolites - Alcohol-Radiolabel

Metabolite	% of Administered Dose	% in Feces
COOH-FENP	2.0-6.7	3.1-10.1
4'-OH-CH_2OH-FENP	1.8-7.1	3.6-10.5
CH_2OH-FENP	9.2-20.1	15.6-29.7
4'-OH-FENP	4.9-10.9	9.2-18.7
Fenpropathrin	12.7-34.3	18.8-53.3
Unknown	2.3-14.4	4.3-21.2

Fecal Metabolites - Acid-Radiolabel

Metabolite	% of Administered Dose	% in Feces
COOH-FENP	1.6-5.0	3.2-7.4
4'-OH-CH_2OH-FENP	1.9-4.4	3.4-6.6
CH_2OH-FENP	8.5-11.6	16.1-20.4
4'-OH-FENP	3.6-10.7	7.2-23.6
Fenpropathrin	16.1-33.4	35.5-53.3
Unknown	4.8-11.8	7.6-17.6

Proposed Metabolic Pathways: A graphic portrayal of the proposed metabolic pathways for fenpropathrin in rats is attached (study report Figure 15, p 122). About 20% of the radiolabel was eliminated as parent compound. The major biotransformations included oxidation at the methyl group of the acid moiety, hydroxylation at the 4'- position of the alcohol moiety, cleavage of the ester linkage, and conjugation with sulfuric acid or glucuronic acid.

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